

## **Methods for Treating Substance Abuse with Cholinesterase Inhibitors**

### **Related Applications**

This application is a continuation under § 120 of PCT/US02/32998 filed October 17, 2002, which claims priority under § 119 to US Provisional Application No. 60/329,529 filed  
5 October 17, 2001, the disclosures of which are incorporated by reference in their entirety.

### **Field of the Invention**

The invention provides methods for treating substance abuse by administering a therapeutically effective amount of at least one cholinesterase inhibitor. A preferred cholinesterase inhibitor is donepezil or ARICEPT®.

### **Background of the Invention**

Every society has used addictive drugs that alter moods, thoughts and/or feelings. Pharmacological advances have also been paralleled by physical and behavioral dependence on drugs that are initially consumed for therapeutic purposes, e.g., OxyContin®. Therefore, the alleviation and eventual withdrawal from undesired physical and/or psychological dependence  
15 and tolerance of an addictive substance has been a challenge. Although there are some methods available for treating withdrawal from addictive substances, there is a great need for safer and more effective treatments.

It would be particularly desirable to provide an effective treatment that could minimize hospitalization or institutionalization of a patient. The treatment must be non-addictive and  
20 provide a favorable side effect profile. It is particularly desired to provide a method that can help or motivate a patient to want to stop taking the addictive substance. It is also desirable to provide a method that would minimize the instances of relapse into abuse of the addictive substance. The invention is directed to these, as well as other, important ends.

### **Summary of the Invention**

25 The invention provides methods for treating substance abuse in a patient by administering an effective amount of at least one cholinesterase inhibitor.

The invention provides methods for treating a patient suffering from withdrawal symptoms caused by cessation from the use of a physically and/or psychologically addictive substance comprising administering an effective amount of at least one cholinesterase inhibitor.

30 The invention provides methods for decreasing the rate of relapse in a patient who had

previously been addicted to a physically and/or psychologically addictive substance comprising administering an effective amount of at least one cholinesterase inhibitor.

The invention provides methods for motivating a patient to stop using a physically and/or psychologically addictive substance by administering an effective amount of at least one  
5 cholinesterase inhibitor.

The invention is described in more detail below.

### **Detailed Description of the Invention**

The invention provides methods for treating substance abuse in a patient by administering an effective amount of at least one cholinesterase inhibitor. The methods of the invention are  
10 applicable to any substances that are abused by patients or that may cause physical and/or psychological dependence (i.e., addiction). Addictive substances may be prescription drugs or street drugs. Addictive substances include, for example, alcohol, opioids, anxiolytic drugs, hypnotic drugs, cocaine, psychedelic agents, marijuana, amphetamines, hallucinogens, phencyclidine, benzodiazepines, and the like. Addictive substances include club drugs, such as  
15 GHB, ketamine, ecstasy, methamphetamine, LSD, and the like.

The invention provides methods for treating a patient suffering from withdrawal symptoms resulting from cessation from the use of an addictive substance comprising administering an effective amount of at least one cholinesterase inhibitor. The withdrawal symptoms of addictive substances are well known in the art. Withdrawal symptoms may  
20 include, for example, cravings for the addictive substance, irritability, insomnia, impatience, restlessness, difficulty concentrating, increased appetite, decreased heart rate, and the like.

The invention provides methods for decreasing the rate of relapse in a patient who had previously been dependent upon or addicted to an addictive substance comprising administering an effective amount of at least one cholinesterase inhibitor.

25 The invention provides methods for motivating or helping a patient to stop using an addictive substance by administering an effective amount of at least one cholinesterase inhibitor.

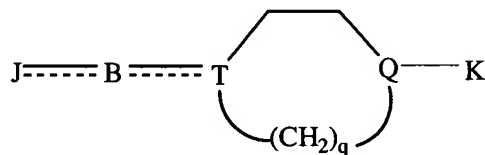
The methods of the invention are preferably administered in conjunction with an educational and/or behavioral modification program to ensure continued abstinence from addictive drugs. The methods of the invention are beneficial to such programs by alleviating the  
30 withdrawal symptoms associated with the cessation of addictive drugs over the course of such programs. The programs may be more effective by focusing on educational and behavioral

modification goals, further reducing the incidence of program non-completion and/or relapse.

“Patient” refers to animals, preferably mammals, more preferably humans. The term “patient” includes adults and children, and includes men and women. Children includes neonates, infants, and adolescents.

5 The methods of the invention are conducted by administering to a patient in need thereof a therapeutically effective amount of at least one cholinesterase inhibitor. The cholinesterase inhibitor can be any known in the art. Exemplary cholinesterase inhibitors include donepezil, tacrine, physostigmine, rivastigmine, galantamine, citicoline, velnacrine maleate, metrifonate, heptastigmine, and the like.

10 In one embodiment, the cholinesterase inhibitor is a compound of formula I, a stereoisomer thereof and/or a pharmaceutically acceptable salt thereof:



wherein J is

- 15 (a) a substituted or unsubstituted group selected from the group consisting of (1) phenyl, (2) pyridyl, (3) pyrazyl, (4) quinolyl, (5) cyclohexyl, (6) quinoxalyl, and (7) furyl;
- (b) a monovalent or divalent group, in which the phenyl may have one or more substituents selected from (1) indanyl, (2) indanonyl, (3) indenyl, (4) indenonyl, 20 (5) indanedionyl, (6) tetralonyl, (7) benzosuberonyl, (8) indanoly, and (9) C<sub>6</sub>H<sub>5</sub>-CO-CH(CH<sub>3</sub>)-;
- (c) a monovalent group derived from a cyclic amide compound;
- (d) a lower alkyl group; or
- (e) a group of R<sup>21</sup>-CH=CH-, in which R<sup>21</sup> is hydrogen or a lower alkoxy carbonyl group;
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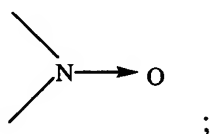
B is -(CHR<sup>22</sup>)<sub>r</sub>-, -CO-(CHR<sup>22</sup>)<sub>r</sub>-, -NR<sup>4</sup>-(CHR<sup>22</sup>)<sub>r</sub>-, -CO-NR<sup>5</sup>-(CHR<sup>22</sup>)<sub>r</sub>-, -CH=CH-(CHR<sup>22</sup>)<sub>r</sub>-, -OCOO-(CHR<sup>22</sup>)<sub>r</sub>-, -OOC-NH-(CHR<sup>22</sup>)<sub>r</sub>-, -NH-CO-(CHR<sup>22</sup>)<sub>r</sub>-, -CH<sub>2</sub>-CO-NH-(CHR<sup>22</sup>)<sub>r</sub>-, -(CH<sub>2</sub>)<sub>2</sub>-NH-(CHR<sup>22</sup>)<sub>r</sub>-, -CH(OH)-(CHR<sup>22</sup>)<sub>r</sub>-, =(CH-CH=CH)<sub>b</sub>-,

$=\text{CH}-(\text{CH}_2)_c-$ ,  $=(\text{CH}-\text{CH})_d=$ ,  $-\text{CO}-\text{CH}=\text{CH}-\text{CH}_2-$ ,  $-\text{CO}-\text{CH}_2-\text{CH}(\text{OH})-\text{CH}_2-$ ,  
 $-\text{CH}(\text{CH}_3)-\text{CO}-\text{NH}-\text{CH}_2-$ ,  $-\text{CH}=\text{CH}=\text{CO}-\text{NH}-(\text{CH}_2)_2-$ ,  $-\text{NH}-$ ,  $-\text{O}-$ ,  $-\text{S}-$ , a dialkylaminoalkyl-  
carbonyl or a lower alkoxy carbonyl;

- 5 wherein  $\text{R}^4$  is hydrogen, lower alkyl, acyl, lower alkylsulfonyl, phenyl, substituted phenyl, benzyl, or substituted benzyl;  $\text{R}^5$  is hydrogen, lower alkyl or phenyl;  $r$  is zero or an integer of about 1 to about 10;  $\text{R}^{22}$  is hydrogen or methyl so that one alkylene group may have no methyl branch or one or more methyl branches;  $b$  is an integer of about 1 to about 3;  $c$  is zero or an integer of about 1 to about 9;  $d$  is zero or an integer of about 1 to about 5;

T is nitrogen or carbon;

- 10 Q is nitrogen, carbon or

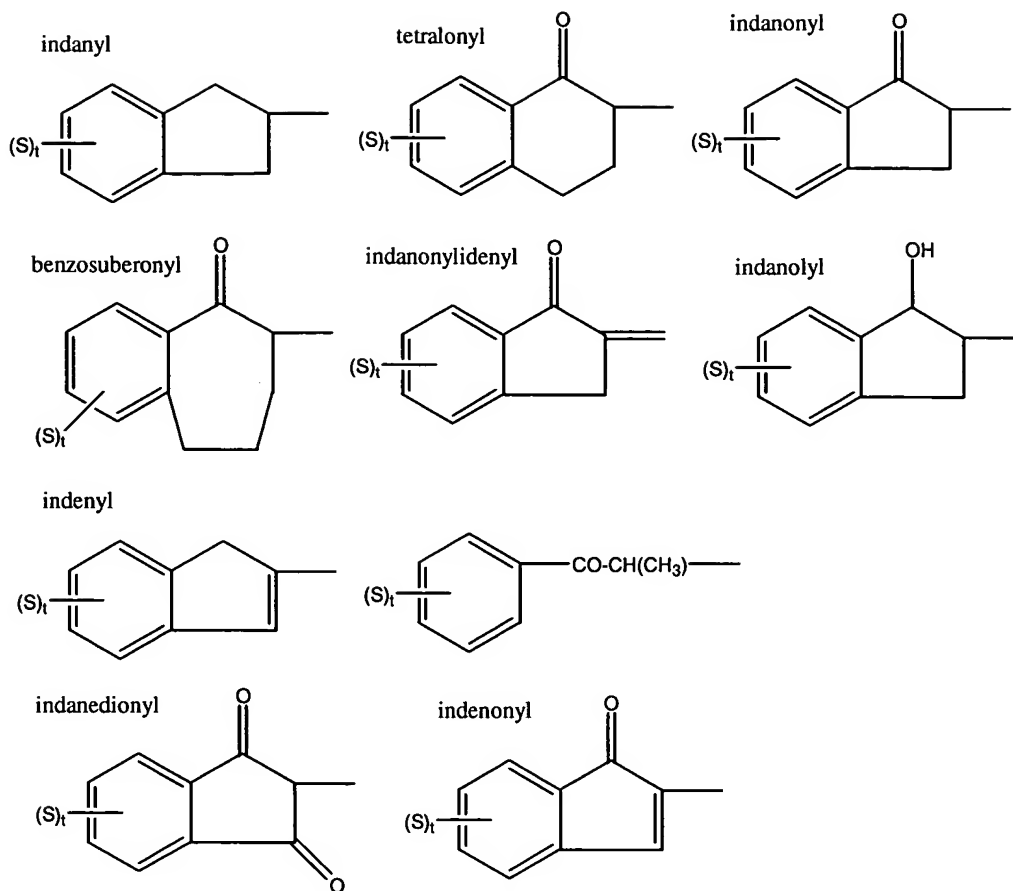


$q$  is an integer of about 1 to about 3;

- K is hydrogen, phenyl, substituted phenyl, arylalkyl in which the phenyl may have a substituent, cinnamyl, a lower alkyl, pyridylmethyl, cycloalkylalkyl, adamantanemethyl, furylmenthyl, cycloalkyl, lower alkoxy carbonyl or an acyl; and
- 15

----- is a single bond or a double bond.

In the compound of formula I, J is preferably (a) or (b), more preferably (b). In the definition of (b), a monovalent group (2), (3) and (5) and a divalent group (2) are preferred. The group (b) preferably includes, for example, the groups having the formulae shown below:



wherein  $t$  is an integer of about 1 to about 4; and each  $S$  is independently hydrogen or a substituent, such as a lower alkyl having 1 to 6 carbon atoms or a lower alkoxy having 1 to 6 carbon atoms. Among the substituents, methoxy is most preferred. The phenyl is most preferred to have 1 to 3 methoxy groups thereon.  $(S)_t$  may form methylene dioxy groups or ethylene dioxy groups on two adjacent carbon atoms of the phenyl group. Of the above groups, indanonyl, indanedionyl and indenyl, optionally having substituents on the phenyl, are the most preferred.

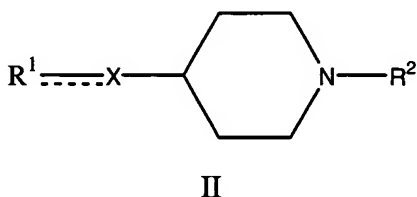
In the definition of  $B$ ,  $-(CHR^{22})_r-$ ,  $-CO-(CHR^{22})_r-$ ,  $=(CH-CH=CH)_b-$ ,  $=CH-(CH_2)_c-$  and  $=(CH-CH)_d=$  are preferable. The group of  $-(CHR^{22})_r-$  in which  $R^{22}$  is hydrogen and  $r$  is an integer of 1 to 3, and the group of  $=CH-(CH_2)_c-$  are most preferable. The preferable groups of  $B$  can be connected with (b) of  $J$ , in particular (b)(2).

The ring containing  $T$  and  $Q$  in formula I can be 5-, 6- or 7-membered. It is preferred that  $Q$  is nitrogen,  $T$  is carbon or nitrogen, and  $q$  is 2; or that  $Q$  is nitrogen,  $T$  is carbon, and  $q$  is 1 or 3; or that  $Q$  is carbon,  $T$  is nitrogen and  $q$  is 2.

It is preferable that  $K$  is a phenyl, arylalkyl, cinnamyl, phenylalkyl or a phenylalkyl

having a substituent(s) on the phenyl.

In preferred embodiments, the cyclic amine compounds of formula I are the piperidine compounds of formula II, a stereoisomer thereof and/or a pharmaceutically acceptable salt thereof:



wherein  $R^1$  is a (1) substituted or unsubstituted phenyl group; (2) a substituted or unsubstituted pyridyl group; (3) a substituted or unsubstituted pyrazyl group; (4) a substituted or unsubstituted quinolyl group; (5) a substituted or unsubstituted indanyl group; (6) a substituted or unsubstituted cyclohexyl group; (7) a substituted or unsubstituted quinoxalyl group; (8) a substituted or unsubstituted furyl group; (9) a monovalent or divalent group derived from an indanone having a substituted or unsubstituted phenyl ring; (10) a monovalent group derived from a cyclic amide compound; (11) a lower alkyl group; or (12) a group of the formula  $R^3-CH=C-$ , where  $R^3$  is a hydrogen atom or a lower alkoxy carbonyl group;

15         $X$  is  $-(CH_2)_n-$ ,  $-C(O)-(CH_2)_n-$ ,  $-N(R^4)-(CH_2)_n-$ ,  $-C(O)-N(R^5)-(CH_2)_n-$ ,  $-CH=CH-(CH_2)_n-$ ,  $-O-C(O)-O-(CH_2)_n-$ ,  $-O-C(O)-NH-(CH_2)_n-$ ,  $-CH=CH-CH=CO-$ ,  $-NH-C(O)-(CH_2)_n-$ ,  $-CH_2-C(O)-NH-(CH_2)_n-$ ,  $-(CH_2)_2-C(O)-NH-(CH_2)_n-$ ,  $-CH(OH)-(CH_2)_n-$ ,  $-C(O)-CH=CH-CH_2-$ ,  $-C(O)-CH_2-CH(OH)-CH_2-$ ,  $-CH(CH_3)-C(O)-NH-CH_2-$ ,  $-CH=CH-C(O)-NH-(CH_2)_2-$ , a dialkylaminoalkylcarbonyl group, a lower alkoxy carbonyl group;

20        where  $n$  is an integer of 0 to 6;  $R^4$  is a hydrogen atom, a lower alkyl group, an acyl group, a lower alkylsulfonyl group, a substituted or unsubstituted phenyl group, or a substituted or unsubstituted benzyl group; and  $R^5$  is a hydrogen atom a lower alkyl group or a phenyl group;

25         $R^2$  is a substituted or unsubstituted phenyl group; a substituted or unsubstituted arylalkyl group; a cinnamyl group; a lower alkyl group; a pyridylmethyl group; a cycloalkylalkyl group; an adamantanemethyl group; or a furoylmethyl group; and

----- is a single bond or a double bond.

The term "lower alkyl group" as used herein means a straight or branched alkyl group

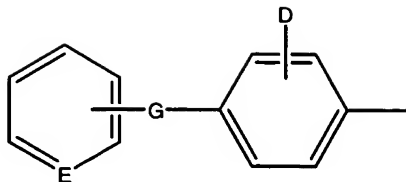
having 1 to 6 carbon atoms. Exemplary “lower alkyl groups” include methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl (amyl), isopentyl, neopentyl, tert-pentyl, 1-methylbutyl, 2-methylbutyl, 1,2-dimethylpropyl, hexyl, isohexyl, 1-methylpentyl, 2-methylpentyl, 3-methylpentyl, 1,1-dimethylbutyl, 1,2-dimethylbutyl, 2,2-dimethylbutyl, 1,3-dimethylbutyl, 2,3-dimethylbutyl, 3,3-dimethylbutyl, 1-ethylbutyl, 2-ethylbutyl, 1,1,2-trimethylpropyl, 1,2,2-trimethylpropyl, 1-ethyl-1-methylpropyl, 1-ethyl-2-methylpropyl, and the like. The lower alkyl group is preferably methyl, ethyl, propyl or isopropyl; more preferably methyl.

Specific examples of the substituents for the substituted or unsubstituted phenyl, pyridyl, pyrazyl, quinolyl, indanyl, cyclohexyl, quinoxalyl and furyl groups in the definition of R<sup>1</sup>

include lower alkyl groups having 1 to 6 carbon atoms, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, and tert-butyl groups; lower alkoxy groups corresponding to the above-described lower alkyl groups, such as methoxy and ethoxy groups; a nitro group; halogen atoms, such as chlorine, fluorine and bromine; a carboxyl group; lower alkoxycarbonyl groups corresponding to the above-described lower alkoxy groups, such as methoxycarbonyl, ethoxycarbonyl, isopropoxycarbonyl, n-propoxycarbonyl, and n-butyloxycarbonyl groups; an amino group; a lower monoalkylamino group; a lower dialkylamino group; a carbamoyl group; acylamino groups derived from aliphatic saturated monocarboxylic acids having 1 to 6 carbon atoms, such as acetylamino, propionylamino, butyrylamino, isobutyrylamino, valerylamino, and pivaloylamino groups; cycloalkyloxycarbonyl groups, such as a cyclohexyloxycarbonyl group; lower alkylaminocarbonyl groups, such as methylaminocarbonyl and ethylaminocarbonyl groups; lower alkylcarbonyloxy groups corresponding to the above-defined lower alkyl groups, such as methylcarbonyloxy, ethylcarbonyloxy, and n-propylcarbonyloxy groups; halogenated lower alkyl groups, such as a trifluoromethyl group; a hydroxyl group; a formyl group; and lower alkoxy lower alkyl groups, such as ethoxymethyl, methoxymethyl and methoxyethyl groups.

The “lower alkyl groups” and “lower alkoxy groups” in the above description of the substituent include all the groups derived from the above-mentioned groups. The substituent may be one to three of them, which may be the same or different.

When the substituent is a phenyl group, the following group is within the scope of the substituted phenyl group:



wherein G is -C(O)-, -O-C(O)-, -O-, -CH<sub>2</sub>-NH-C(O)-, -CH<sub>2</sub>-O-, -CH<sub>2</sub>-SO<sub>2</sub>-, -CH(OH)-, or -CH<sub>2</sub>-S(→O)-; E is a carbon or nitrogen atom; and D is a substituent.

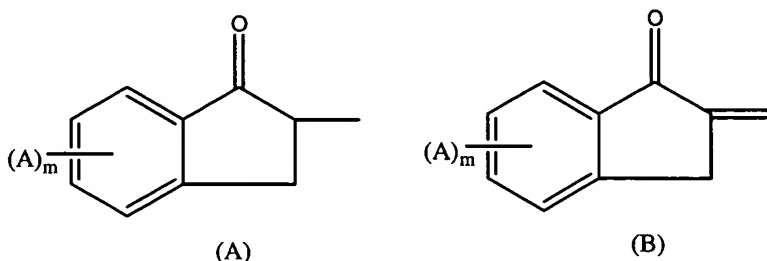
Preferred examples of the substituents (i.e., "D") for the phenyl group include lower alkyl, lower alkoxy, nitro, halogenated lower alkyl, lower alkoxycarbonyl, formyl, hydroxyl, and lower alkoxy lower alkyl groups, halogen atoms, and benzyol and benzylsulfonyl groups. The substituent may be two or more of them, which may be the same or different.

Preferred examples of the substituent for the pyridyl group include lower alkyl and amino groups and halogen atoms.

Preferred examples of the substituent for the pyrazyl group include lower alkoxycarbonyl, carboxyl, acylamino, carbamoyl, and cycloalkyloxycarbonyl groups.

With respect to R<sup>1</sup>, the pyridyl group is preferably a 2-pyridyl, 3-pyridyl, or 4-pyridyl group; the pyrazyl group is preferably a 2-pyrazinyl group; the quinolyl group is preferably a 2-quinolyl or 3-quinolyl group; the quinoxalinyl group is preferably a 2-quinoxalinyl or 3-quinoxalinyl group; and the furyl group is preferably a 2-furyl group.

Specific examples of preferred monovalent or divalent groups derived from an indanone having an unsubstituted or substituted phenyl ring include those represented by formulas (A) and (B):



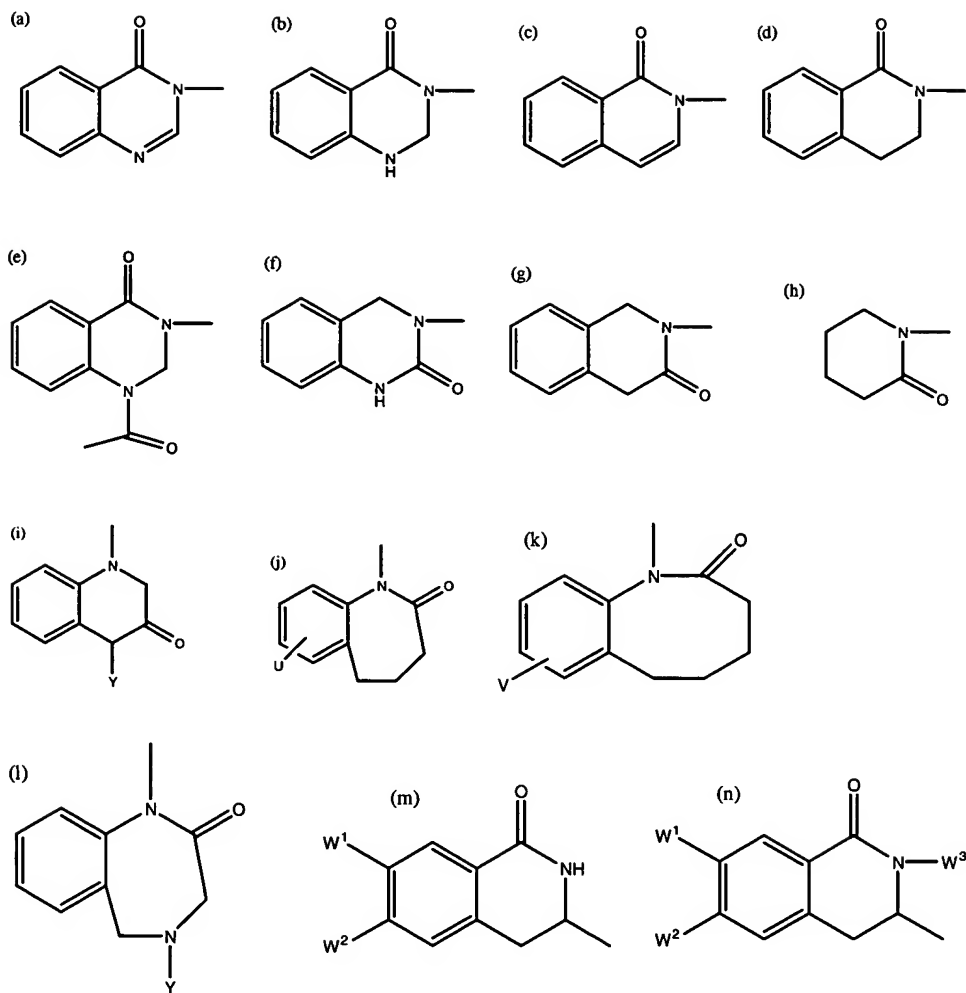
where m is an integer of from 1 to 4, and each A is independently a hydrogen atom, a lower alkyl group, a lower alkoxy group, a nitro group, a halogen atom, a carboxyl group, a lower alkoxycarbonyl group, an amino group, a lower monoalkylamino group, a lower dialkylamino group, a carbamoyl group, an acylamino group derived from aliphatic saturated



monocarboxylic acids having 1 to 6 carbon atoms, a cycloalkyloxycarbonyl group, a lower alkylaminocarbonyl group, a lower alkylcarbonyloxy group, a halogenated lower alkyl group, a hydroxyl group, a formyl group, or a lower alkoxy lower alkyl group; preferably a hydrogen atom, a lower alkyl group or a lower alkoxy group; most preferably the indanone group is unsubstituted or substituted with 1 to 3 methoxy groups.

Examples of the monovalent group derived from a cyclic amide compound include quinazalone, tetrahydroisoquinolinone, tetrahydrobenzodiazepinone, and hexahydrobenzazocinone. However, the monovalent group may be any one having a cyclic amide group in the structural formula thereof, and is not limited to the above-described specific examples. The cyclic amide group may be one derived from a monocyclic or condensed heterocyclic ring. The condensed heterocyclic ring is preferably one formed by condensation with a phenyl ring. In this case, the phenyl ring may be substituted with a lower alkyl group having 1 to 6 carbon atoms, preferably a methyl group, or a lower alkoxy group having 1 to 6 carbon atoms, preferably a methoxy group.

Preferred examples of the monovalent group include the following:



In the above formulae, Y is a hydrogen atom or a lower alkyl group; V and U are each a hydrogen atom or a lower alkoxy group (preferably dimethoxy); W<sup>1</sup> and W<sup>2</sup> are each a hydrogen atom, a lower alkyl group, or a lower alkoxy group; and W<sup>3</sup> is a hydrogen atom or a lower alkyl group. The right hand ring in formulae (j) and (l) is a 7-membered ring, while the right hand ring in formula (k) is an 8-membered ring.

The most preferred examples of the above-defined R<sup>1</sup> include a monovalent group derived from an indanone having an unsubstituted or substituted phenyl group and a monovalent group derived from a cyclic amide compound.

The most preferred examples of the above-defined X include -(CH<sub>2</sub>)<sub>n</sub>-, an amide group, or groups represented by the above formulae where n is 2. Thus, it is most preferred that any portion of a group represented by the formula R<sup>1</sup>-----X----- have a carbonyl or amide group.

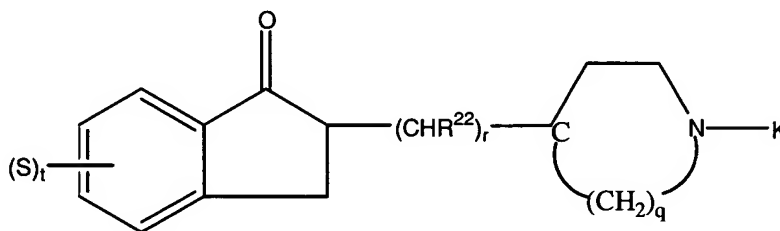
The substituents involved in the expressions “a substituted or unsubstituted phenyl group” and “a substituted or unsubstituted arylalkyl group” in the above definition of  $R^2$  are the same substituents as those described for the above definitions of a phenyl group, a pyridyl group, a pyrazyl group, a quinolyl group, an indanyl group, a cyclohexyl group, a quinoxalyl group or a furyl group in the definition of  $R^1$ .

The term “arylalkyl group” is intended to mean an unsubstituted benzyl or phenethyl group or the like.

Specific examples of the pyridylmethyl group include 2-pyridylmethyl, 3-pyridylmethyl, and 4-pyridylmethyl groups.

Preferred examples of  $R^2$  include benzyl and phenethyl groups. The symbol  $\text{-----}$  means a double or single bond. The bond is a double bond only when  $R^1$  is the divalent group (B) derived from an indanone having an unsubstituted or substituted phenyl ring, while it is a single bond in other cases.

In preferred embodiments, the compound of formula II is a compound of formula III, a stereoisomer thereof and/or a pharmaceutically acceptable salt thereof:



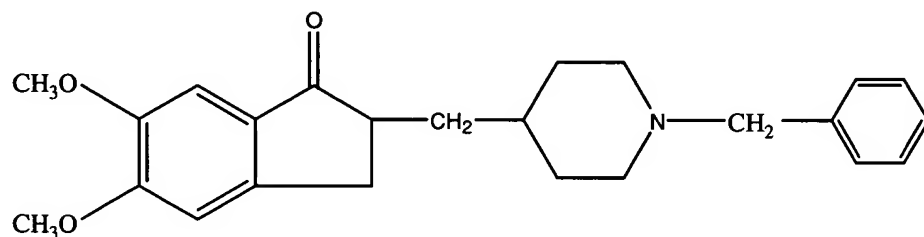
III

wherein  $r$  is an integer of about 1 to about 10; each  $R^{22}$  is independently hydrogen or methyl;  $K$  is a phenalkyl or a phenalkyl having a substituent on the phenyl ring; each  $S$  is independently a hydrogen, a lower alkyl group having 1 to 6 carbon atoms or a lower alkoxy group having 1 to 6 carbon atoms;  $t$  is an integer of 1 to 4;  $q$  is an integer of about 1 to about 3; with the proviso that  $(S)_t$  can be a methylenedioxy group or an ethylenedioxy group joined to two adjacent carbon atoms of the phenyl ring.

In preferred embodiments, the compound of formula III is 1-benzyl-4-((5,6-dimethoxy-1-indanon)-2-yl)methylpiperidine; 1-benzyl-4-((5,6-dimethoxy-1-indanon)-2-ylidenyl)methylpiperidine; 1-benzyl-4-((5-methoxy-1-indanon)-2-yl)methylpiperidine; 1-benzyl-

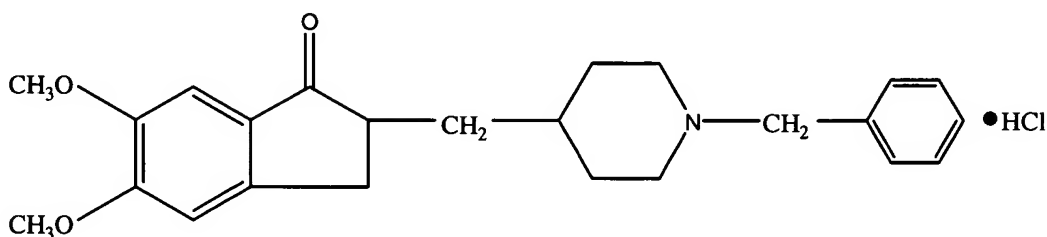
4-((5,6-diethoxy-1-indanon)-2-yl)methylpiperidine; 1-benzyl-4-((5,6-methnylenedioxy-1-indanon)-2-yl)methylpiperidine; 1-(m-nitrobenzyl)-4-((5,6-dimethoxy-1-indanon)-2-yl)methylpiperidine; 1-cyclohexylmethyl-4-((5,6-dimethoxy-1-indanon)-2-yl)methylpiperidine; 1-(m-fluorobenzyl)-4-((5,6-dimethoxy-1-indanon)-2-yl)methylpiperidine; 1-benzyl-4-((5,6-dimethoxy-1-indanon)-2-yl)propylpiperidine; 1-benzyl-4-((5-isopropoxy-6-methoxy-1-indanon)-2-yl)methylpiperidine; 1-benzyl-4-((5,6-dimethoxy-1-oxoindanon)-2-yl)propenylpiperidine; or pharmaceutically acceptable salts thereof.

In more preferred embodiments, the compound of formula III is 1-benzyl-4-((5,6-dimethoxy-1-indanon)-2-yl)methylpiperidine, a stereoisomer thereof and/or a pharmaceutically acceptable salt thereof which is represented by formula IV:



IV.

In the most preferred embodiment, the compound of formula III is 1-benzyl-4-((5,6-dimethoxy-1-indanon)-2-yl)methylpiperidine hydrochloride or a stereoisomer thereof, which is also known as donepezil hydrochloride or ARICEPT® (Eisai Inc., Teaneck, NJ), and which has formula IVa:

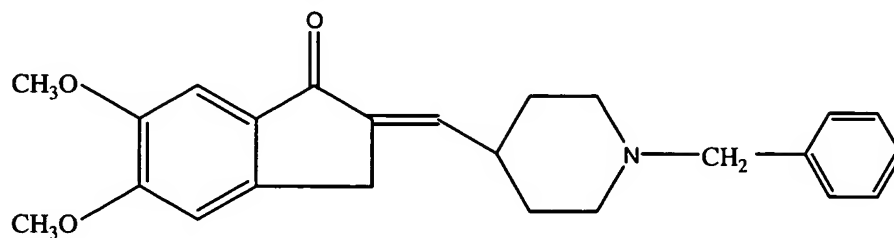


IVa.

The compounds of the invention may have an asymmetric carbon atom(s), depending upon the substituents, and can have stereoisomers, which are within the scope of the invention. For example, donepezil hydrochloride can be in the forms described in Japanese Patent Application Nos. 4-187674 and 4-21670, the disclosures of which are incorporated by reference

herein in their entirety.

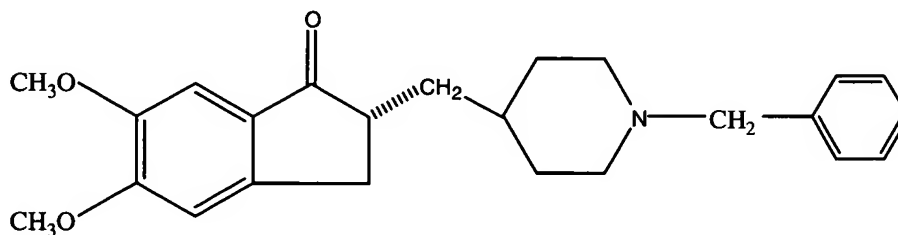
Japanese Patent Application No. 4-187674 describes a compound of formula V:



V

5 which can be in the form of a pharmaceutically acceptable salt, such as a hydrochloride salt.

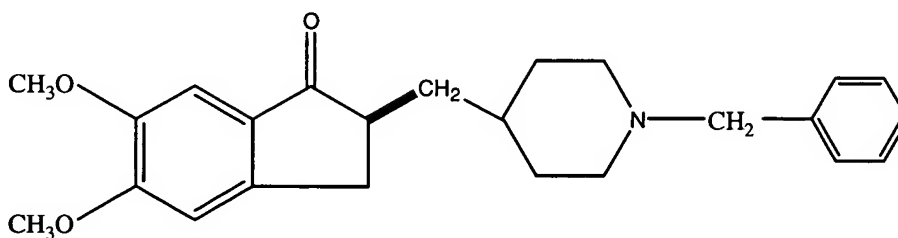
Japanese Patent Application No. 4-21670 describes compounds of formula VI:



VI

which can be in the form of a pharmaceutically acceptable salt, such as a hydrochloride salt; and

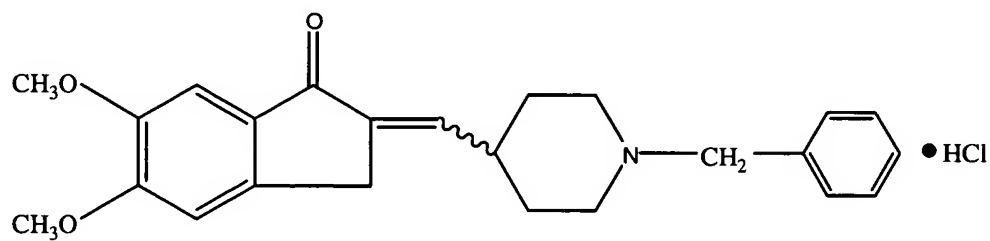
10 compounds of formula VII:



VII

which can be in the form of a pharmaceutically acceptable salt, such as a hydrochloride salt; and

compounds of formula VIII:



VIII.

As described above, the compounds of the invention can be administered in the form of a pharmaceutically acceptable salt. Pharmaceutically acceptable salts are known in the art and include those of inorganic acids, such as hydrochloride, sulfate, hydrobromide and phosphate; and those of organic acids, such as formate, acetate, trifluoroacetate, methanesulfonate, benzenesulfonate and toluenesulfonate. When certain substituents are selected, the compounds of the invention may form, for example, alkali metal salts, such as sodium or potassium salts; alkaline earth metal salts, such as calcium or magnesium salts; organic amine salts, such as a salt with trimethyl-amine, triethylamine, pyridine, picoline, dicyclohexylamine or N,N'-dibenzylethylene-diamine. One skilled in the art will recognize that the compounds of the invention can be made in the form of any other pharmaceutically acceptable salt.

The cholinesterase inhibitors of the invention can be prepared by processes that are known in the art and described, for example, in U.S. Patent No. 4,895,841, WO 98/39000, and Japanese Patent Application Nos. 4-187674 and 4-21670, the disclosures of each of which are incorporated by reference herein in their entirety. Donepezil hydrochloride, a preferred cholinesterase inhibitor for use in the methods described herein, is commercially available as ARICEPT® from Eisai Inc., Teaneck, NJ.

The dosage regimen for treating the diseases described herein with the cholinesterase inhibitors described herein is selected in accordance with a variety of factors, including the age, weight, sex, and medical condition of the patient, the severity of the disease, the route of administration, pharmacological considerations such as the activity, efficacy, pharmacokinetic and toxicology profiles of the particular cholinesterase inhibitor used, whether a drug delivery system is used and whether the cholinesterase inhibitor is administered as part of a drug combination.

In preferred embodiments, the cholinesterase inhibitors of the invention are administered in the methods described herein in doses of about 0.1 milligram to about 300 milligrams per day, preferably about 1 milligram to about 100 milligrams per day, more preferably about 5 milligrams to about 10 milligrams per day. The doses can be administered in one to four portions over the course of a day, preferably once a day. One skilled in the art will recognize that when the cholinesterase inhibitors of the invention are administered to children, the dose may be smaller than the dose administered to adults, and that the dose can be dependent upon the

size and weight of the patient. In preferred embodiments, a child can be administered the cholinesterase inhibitors of the invention in doses of about 0.5 milligrams to about 10 milligrams per day, preferably about 1 milligram to about 3 milligrams per day. The methods of the invention may be used to treat children (e.g., neonates) who are born addicted to drugs because of their mother's addiction.

In preferred embodiments of the methods described herein, a physician can administer patients donepezil hydrochloride, which is commercially available as ARICEPT® (Eisai Inc., Teaneck, NJ), as film-coated tablets containing 5 milligrams donepezil hydrochloride or 10 milligrams donepezil hydrochloride. The tablets can be administered one to about four times a day. In preferred embodiments, one 5 milligram or one 10 milligram ARICEPT® tablet is administered once a day for the methods described herein. One skilled in the art will appreciate that when donepezil hydrochloride is administered to children, the dose may be smaller than the dose that is administered to adults. In preferred embodiments, a child can be administered donepezil hydrochloride in doses of about 0.5 milligrams to about 10 milligrams per day, preferably about 1 milligram to about 3 milligrams per day.

The cholinesterase inhibitors of the invention can be administered orally, topically, parenterally, by inhalation (nasal or oral), or rectally in dosage unit formulations containing conventional nontoxic pharmaceutically acceptable carriers, adjuvants, and vehicles as desired. The term parenteral as used herein includes subcutaneous, intravenous, intramuscular, intrasternal injection, or infusion techniques. Preferably, the cholinesterase inhibitors of the invention are orally administered as tablets. When administered to children, the cholinesterase inhibitors of the invention are preferably orally administered in a liquid dosage form.

Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions may be formulated according to the known art using suitable dispersing or wetting agents, suspending agents (e.g., methylcellulose, Polysorbate 80, hydroxyethylcellulose, acacia, powdered tragacanth, sodium carboxymethylcellulose, polyoxyethylene sorbitan monolaurate and the like), pH modifiers, buffers, solubilizing agents (e.g., polyoxyethylene hydrogenated castor oil, Polysorbate 80, nicotinamide, polyoxyethylene sorbitan monolaurate, Macrogol, an ethyl ester of castor oil fatty acid, and the like) and preservatives. The sterile injectable preparation may also be a sterile injectable solution or suspension in a nontoxic parenterally

acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be used are water, Ringer's solution, and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally used as a solvent or suspending medium. For this purpose any bland fixed oil may be used including synthetic  
5 mono- or diglycerides, in addition, fatty acids such as oleic acid find use in the preparation of injectables. The preparations can be lyophilized by methods known in the art.

Solid dosage forms for oral administration may include chewing gum, capsules, tablets, sublingual tablets, powders, granules and gels; most preferably tablets. In such solid dosage forms, the active compound may be admixed with one or more inert diluents such as lactose or  
10 starch. As is normal practice, such dosage forms may also comprise other substances including lubricating agents such as magnesium stearate. In the case of capsules, tablets, and pills, the dosage forms may also comprise buffering agents. The tablets can be prepared with enteric or film coatings, preferably film coatings.

In addition to the active ingredient, the tablets preferably comprise lactose monohydrate,  
15 corn starch, microcrystalline cellulose, hydroxypropyl cellulose, and magnesium stearate; while the film-coating on the tablet preferably comprises talc, polyethylene glycol, hydroxypropyl methylcellulose, titanium dioxide, and, optionally, other coloring agents, such as yellow iron oxide.

Liquid dosage forms for oral administration can include pharmaceutically acceptable  
20 emulsions, solutions, suspensions, and syrups containing inert diluents commonly used in the art, such as water. Such compositions can also comprise adjuvants, such as wetting agents, emulsifying and suspending agents, and sweetening, flavoring, and perfuming agents.

For administration by inhalation, the compositions of the invention can be delivered from an insufflator, a nebulizer or a pressured pack or other convenient mode of delivering an aerosol  
25 spray. Pressurized packs can include a suitable propellant. Alternatively, for administration by inhalation, the compositions can be administered in the form of a dry powder composition or in the form of a liquid spray.

Suppositories for rectal administration can be prepared by mixing the active compounds with suitable nonirritating excipients such as cocoa butter and polyethylene glycols that are solid



at room temperature and liquid at body temperature.

For topical administration to the epidermis, the cholinesterase inhibitors may be formulated as ointments, creams or lotions, or as the active ingredient of a transdermal patch. The cholinesterase inhibitors may also be administered via iontophoresis. Ointments, creams  
5 and lotions may be formulated with an aqueous or oily base with the addition of suitable thickening and/or gelling agents. Alternatively, ointments, creams and lotions may be formulated with an aqueous or oily base and may also contain one or more emulsifying agents, stabilizing agents, dispersing agents, suspending agents, thickening agents, and/or coloring agents. As creams or lotions, the cholinesterase inhibitors may be mixed to form a smooth,  
10 homogeneous cream or lotion with, for example, one or more of a preservative (e.g., benzyl alcohol 1% or 2% (wt/wt)), emulsifying wax, glycerin, isopropyl palmitate, lactic acid, purified water, sorbitol solution. Such topically administrable compositions may contain polyethylene glycol 400. To form ointments, the cholinesterase inhibitors may be mixed with one or more of a preservative (e.g., benzyl alcohol 2% (wt/wt)), petrolatum, emulsifying wax, and Tenox (II)  
15 (e.g., butylated hydroxyanisole, propyl gallate, citric acid, propylene glycol). Woven pads or rolls of bandaging material, e.g., gauze, may be impregnated with the transdermally administrable compositions for topical application.

The cholinesterase inhibitors may also be topically applied using a transdermal system, such as one of an acrylic-based polymer adhesive with a resinous crosslinking agent impregnated  
20 with the cholinesterase inhibitors and laminated to an impermeable backing. For example, the cholinesterase inhibitors may be administered in the form of a transdermal patch, such as a sustained-release transdermal patch. Transdermal patches may include any conventional form such as, for example, an adhesive matrix, a polymeric matrix, a reservoir patch, a matrix- or monolithic-type laminated structure, and are generally comprised of one or more backing layers,  
25 adhesives, penetration enhancers, and/or rate-controlling membranes. Transdermal patches generally have a release liner which is removed to expose the adhesive/active ingredient(s) prior to application. Transdermal patches are described in, for example, U.S. Patent Nos. 5,262,165, 5,948,433, 6,010,715 and 6,071,531, the disclosures of which are incorporated by reference herein in their entirety.

30 While the cholinesterase inhibitors of the invention can be administered as the sole active pharmaceutical agent in the methods described herein, they can also be used in combination with

one or more compounds which are known to be therapeutically effective against the specific disease that one is targeting for treatment.

Each of the patents and publications cited herein are incorporated by reference herein in their entirety.

- 5           It will be apparent to one skilled in the art that various modifications can be made to the invention without departing from the spirit or scope of the appended claims.